in patients with valvular aortic stenosis. Second, the stepped and sequential LVPO induced in the present study is unlikely to completely represent the duration, pattern, and magnitude that occur in clinical forms of LVPO. Nevertheless, this model of LVPO demonstrated significant phenotypic similarities to clinical observations of LVPO in patients in terms of myocardial ECM remodeling and LV diastolic dysfunction. The model system and paradigms identified in this article may provide a means to identify the mechanisms that give rise to pathologic ECM remodeling and the potential point of irreversible ECM remodeling, and thereby improve the timing and treatment approaches for elimination of LVPO stimulus.

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Discussion

Dr Joseph Schmoker *(Burlington, Vt)*. I have no disclosures. My questions pertain to the miR-1 and 133 that you studied. In the mouse model, the transverse aortic constriction (TAC) model, both are actually antihypertrophic and overexpression of miR-133 is associated with down-regulation of collagen in cultured fibroblasts. So I'm curious how you interpret this relative to the opposite findings in your large animal model. In addition, did you perform microarray analysis on myocardium to broaden your miR phenotype?

Dr Yarbrough. We have just begun our initial assessments with respect to miRs. We anticipate performing microarray analysis to broaden the miR phenotype. I agree these initial preliminary miR data are at odds with the relatively small amount of data that exist in the literature with respect to this topic.

At this time, we believe that miR-133 in particular may inhibit collagen 1A1 and 3A1. Our theory is that with up-regulation of miR-133, there is inhibition of collagen 1A1 and 3A1 expression. That would account for the lack of increased collagen expression

noted in the study. In summary, we believe the increased collagen content observed in the study was secondary to increased collagen stability and resistance to degradation as opposed to increased collagen expression. With prolongation of the animal model, we may see a reduction in miR-133 and miR-1 levels that will then ''release'' some of the inhibition on the collagen 1A1 and 3A1 genes. That may then lead to a robust increase in collagen expression, counter to what we're seeing at this point in time at 1 month.

Dr Schmoker. My final question is related to how the control animals were handled at the terminal data collection. My understanding from the article is that the controls were not violated from the standpoint of manipulation of the heart during final data collection. Knowing that both miR-1 and 133 can be induced with myocardial ischemia, could subendocardial ischemia incurred from surgical handling and manipulation during terminal data collection be responsible for the differences in miR expression in the experimental group relative to controls?

Dr Yarbrough. Perhaps, but I don't believe that is likely. We performed microsphere studies on both the control and the instrumented animals and showed no difference in perfusion with respect to microsphere data collected from the endocardium, myocardium, or epicardium. Thus, I don't think submyocardial ischemia was likely.